UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/822,161	03/30/2001	Michael Detmar	MGH 1512 CIP	6294

21874 7590 08/16/2005

EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
HARRIS, ALANA M	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 08/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/822,161	DETMAR ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *25 May 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

3.0.0
3.0.0

DETAILED ACTION

Response to Arguments and Amendments

1. Claims 1-5, 7, 22 and 23 are pending.

Claim 1 has been amended.

Claims 1-5, 7, 22 and 23 are examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-5, 7, 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants broadly claim a method for treating a disorder with thrombospondin-2 (TSP-2) or a fragment thereof wherein a cell-matrix structure comprises a matrix with cells that stably express TSP-2, or a fragment thereof wherein the fragment comprises

at least 10 contiguous amino acids of a procollagen domain of TSP-2 or a Type I repeat of TSP-2. Applicants' method encompasses portions of TSP-2 yet to be characterized and disclosed as rendering anti-angiogenic activity. The written description is not commensurate in scope with claims drawn to a method implementing uncharacterized portions and fragments of TSP-2.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

With the exception of full length TSP-2, a procollagen domain of TSP-2 in its entirety,a Type I repeat of TSP-2 in its entirety, and those TSP-2 molecules defined in the art that maintain antiangiogenic activity (i.e. fragment defined in Hahn et al., enclosed in the instant Action) the skilled artisan cannot envision the detailed structure or function of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Likewise, the skilled artisan cannot envision the detailed structure or function of the plethora of genes that may be induced by three distinct proteins. Adequate written description requires more than a mere statement that it is part of the

invention and a reference to a potential method of isolating it. The polypeptides and molecules germane to the methodology itself are required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement, which defines a genus of nucleic acids by only their functional activity, does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

At the time the application was filed Applicants only had possession of full length TSP-2, a procollagen domain of TSP-2 in its entirety and a Type 1 repeat of TSP-2 in its entirety to be implemented in the manner suggested by the specification and the claims. The specification does not evidence the claimed method conducted with the uncharacterized and undetermined fragments and portions of TSP-2, procollagen domain of TSP-2 and a Type 1 repeat of TSP-2. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. Accordingly, in the absence of sufficient recitation

of distinguishing identifying functional characteristics, the specification does not provide adequate written description of the claimed genus. The specification does not teach any structure of a fragment comprising at least 10 contiguous amino acids of TSP-2, a procollagen domain of TSP-2 or Type 1 repeat of TSP-2 capable of inhibiting or regressing excessive tissue proliferation.

There is insufficient support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

The full breadth of the claims does not meet the written description provision of 35 U.S.C. 112, first paragraph.

5. Claims 1-5, 7, 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating tumor inhibition and angiogenesis of tissue treatable by TSP-2, a procollagen domain of TSP-2 or three Type I repeats of TSP-2 in an amount effective to inhibit or regress excessive tissue proliferation, does not reasonably provide enablement for arbitrary fragments comprising at least 10 contiguous amino acids of TSP-2 or a procollagen domain of TSP-2 or Type I repeat of TSP-2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants' specification supports the use of a TSP-2 retroviral transfection system for the overexpression of the angiogenesis and tumor growth inhibitor and the

subsequent implantation of the generated TSP-2 biodegradable polymer graft into nude mice, see page 30, line 3-32 and Figure 1. The TSP-2 transfected fibroblasts bioimplant continually expressed and secreted TSP-2 and was challenged by cancer cells injected into flanks of mice, see page 32, lines 15-24. "[T]umor growth was significantly inhibited...by more than 60% in mice bearing [said] TSP-2 secreting bioimplants", see Figures 2A-2C and page 33, lines 1-18.

The art substantiates Applicants' findings of injection of TSP-2 transfected clones into nude mice results in pronounced inhibition of tumor growth, see abstract and bridging paragraph of pages 14892 and 14893 of Streit et al. (PNAS 96(26): 14888-14893, 21 December 1999) and Tokunaga et al. (British Journal of Cancer 79(2): 354-359, 1999). The art also provides support for effective inhibition of tumor growth and angiogenesis using a N-terminal fragment of TSP-2 (NfTSP2) which contains the three type I repeats of TSP-2, see Hahn et al., page 739, Introduction section and page 743, column 1, second paragraph of Discussion section (Gene Therapy 11: 739-745, 15 January 2004). However, neither the specification nor the art provide for a method treating a multitude of disorders characterized by proliferation of tissue (i.e. restenosis, endometriosis) with fragments of at least 10 contiguous amino acids of a procollagen domain of TSP-2 or a type I repeat of TSP-2. Armstrong and Bornstein have noted that sequences in the N- and C-terminal domains have pro-angiogenic effects, see abstract, Armstrong and Bornstein (Matrix 22: 63-71, 2003). And Streit notes that at the time of the claimed invention active sites within the procollagen-like domain of TSP-2 had yet to be established, see bridging paragraph of pages 14892 and 14893. Moreover, as

recent as January 2004, Hahn while establishing "...intratumoral injection of a syngeneic cell expressing NfTSP2 or recombinant adenovirus expressing NfTSP2 to carcinomas potently inhibited tumor growth..." also delivers cautionary advice noting many anti-angiogenesis strategies is limited due to technical difficulties, see page 739, paragraph before Results section and page 743, column 2, last paragraph.

One of ordinary skill in the art would cautiously assume that the three type I repeats and procollagen domain of TSP-2 would also mediate inhibitory effect on migration of endothelial cells (EC) as does TSP-1, however one cannot extrapolate these teachings to provide enablement for fragments and portions comprising at least 10 contiguous amino acids of TSP-2, a procollagen domain of TSP-2 or type I repeat of TSP-2 to be effective to inhibit or regress arbitrary excessive tissue proliferation in a plethora of disorders listed in claim 2 broadly encompassed by claim 1.

Considering unpredictability in the cancer treatment art, broad scope of claims, insufficient guidance with regard to various recited cancer treatments with various claimed products, it is maintained that undue experimentation would be required to practice the invention as claimed.

Maintained Rejection

Claim Rejections - 35 USC § 103

6. The rejection of claims 1-5, 7, 22 and 23 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent number 6,558,422 B1 (effective filing date March 26, 1999), and further in view of U.S. Patent number 5,759,830 (issued June 2, 1998/ IDS

reference BA, submitted August 22, 2002) and Gilbert et al. (Transplantation, 56(2): 423-427, August 1993/ IDS reference AD, submitted August 22, 2002) is maintained.

Applicants assert the primary reference, U.S. Patent number 6,558,422 is not entitled to the priority date of its provisional document, 60/126,545 filed March 26, 1999 because Applicants believe the document is silent with respect to TSP-2 and only discloses the schematic diagram entitled "Process Overview", see Remarks filed May 25, 2005, page 5, section A. Further arguments attest patent '422 does not teach or suggest the biologically active substance is a cell and "Vacanti's and Gilbert's finding of increased angiogenesis and fibrous network growth would have precluded the person of ordinary skill in the art from relying upon their teachings in developing a delivery system...based on Baker, since the latter instead advocates reduced angiogenesis and fibrous capsule growth.", see pages 6 and 7, section B. These arguments and points of view have been carefully considered, but found unpersuasive.

The provisional application affords patent '422 sufficient written description and support and Applicants are reminded that U.S. patents are presumed enabling. The art at the time of the claimed invention supports the intrinsic activity of thrombospondin-2 to inhibit angiogenesis *in vitro* and *in vivo*, see page 330, Discussion section of Volpert et al. (Biochemical and Biophysical Research Communications 217(1): 326-332, 5 December 1995). The art clearly established thrombospondin-2's ability to act as an inhibitor of angiogenesis as early as 1995, see page 331, paragraph before Acknowledgments section.

The provisional document teaches the manufacture of medical materials

containing thrombospondins to be implanted into humans, see Summary of the Invention and Background sections. Intrinsically, one of ordinary skill at the time of the claimed invention would reasonably postulate angiogenesis would be inhibited by thrombospondin-2 based on the level of the skill in the art at the time of the claimed invention. These facts support patent '422, wherein it is taught rats were treated with implantable devices, disks containing thrombospondin-2 (TSP-2) wherein angiogenesis and fibrous capsule measurements were reduced, see column 11, lines 5-22; column 12, line 52-column 13, line 14; and Table 5 in column 13. It does follow that the '422 patent does not teach the implantation of a cell-matrix structure wherein the cells are fibroblasts, tissue specific cells or of a different cell type than the tissue that has proliferated and the cells are genetically altered to produce TSP-2 or a fragment thereof. But the teachings of patent '830 and Gilbert readily address those issues with motivation to combine with the primary reference, patent '422. Given the teachings in the art at the time of the claimed invention one of ordinary skill in the art would "rule out" TSP-2 as an inhibitor of angiogenesis.

U.S. Patent #5,759,830 does teach the implementation of cells including tissue specific and fibroblastic cells for the assembly of fibrous cell scaffolds useful in implantation, see column 4, lines 15-20; column 6, lines 21-34; bridging paragraph of columns 11 and 12. The cells can be manipulated by those skilled in the art of genetic engineering in order to introduce new genes to make absent protein products, see column 9, lines 20-32.

Moreover, Gilbert teaches the cell transplantation of genetically altered cells on

fibrous biodegradable polymer scaffolds, see title and abstract. The system is capable of delivering desirable proteins secreted by genetically modified fibroblast cells. "The polymer scaffold allows precise surgical manipulation and site-specific transplantation with subsequent incorporation of the transduced cells into the native tissue over time.", see bridging paragraph of pages 423 and 424.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of both patents and Gilbert in order to treat a disorder characterized by excessive proliferation of tissue with an implantable cell-matrix structure having attached thereto cells that stably express TSP-2 or a fragment thereof able to inhibit or regress excessive tissue proliferation. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in both patents and Gilbert based on the successful treatment of rats in which angiogenesis and fibrous growth were reduced, as well as the implicit teaching that biologically active substances can be used to form layers within indention surfaces and on implantable medical devices placed within a living body, see patent '422, column 4, lines 1-25; column 5, lines 11-19. It is within the Examiner's purview that substances that form layers are inclusive of cells. Moreover, patent '830 presents information stating the taught method is useful both *in vivo* and *in vitro* and medical conditions can be corrected by insertion of genes, see column 22, lines 16-27; column 9, lines 20-32. Likewise, Gilbert suggests "[t]he application of cell transplantation and retroviral gene transfer technologies may lead to the eventual cure of many gene product deficiencies resulting from a single gene defect...", page 425,

column 2, first paragraph of the Discussion section.

For the reasons of record and set forth above one of ordinary skill in the art would have been motivated to combine the teachings of all the references for the successful treatment of any disorder characterized by excessive proliferation of tissue based upon the accomplished treatment in patent '422 and the level of knowledge in the area of genetic engineering at the time of the claimed invention was made.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571) 272-0831. The examiner works a flexible schedule, however she can normally be reached between the hours of 6:30 am to 5:30 pm with the alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

Alana M. Harris, Ph.D.
04 August 2005